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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
OLSON, ERIC	

ART UNIT	PAPER NUMBER
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,149	GRAHAM ET AL.	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6 and 8-14* is/are pending in the application.

4a) Of the above claim(s) *6 and 8-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This office action is a response to applicant's communication submitted September 10, 2007 wherein claims 5 and 7 are cancelled. This application is a national stage application of PCT/GB03/03562, filed August 14, 2003, which claims priority to foreign application GB0218811.8, filed August 14, 2002.

Election/Restrictions

Applicant's election with traverse of group I, drawn to the compound morphine-6-glucuronide hydrobromide, filed September 10, 2007, is acknowledged. Applicant's arguments of record with respect to the aforementioned traversal are acknowledged and found to be not persuasive to remove the requirement for restriction. As mentioned earlier, the alleged improved stability of the claimed compound is applicable only to methods of storing the compound, and not to methods of making or using the compound. Therefore, the methods of instant claims 6 and 8-14 are not expected to be affected in any unexpected manner by the substitution of the bromide counterion for another similar inorganic counterion such as chloride or sulfate. Therefore the requirement for restriction is deemed proper and made **FINAL**.

Claims 6 and 8-14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **with** traverse in the reply filed on September 10, 2007.

Claims 1-4 are pending in this application and examined on the merits herein.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hille et al. (US patent 5705186, cited in PTO-1449) in view of Gao et al. (US patent publication 2003/0050257, cited in PTO-892) in view of Remington. (Reference included with PTO-892) Hille et al. discloses transdermal compositions comprising morphine-6-glucuronide or its salts. (column 1, lines 45-55) Although all pharmaceutically acceptable salts are suitable for this invention, the hydrochloride salt is preferred. (column 3, lines 22-25) Hille et al. does not disclose a hydrobromide salt of morphine-6-glucuronide.

Gao et al. discloses a number of glycosylated morphine derivatives, including 6-glucuronide adducts. (p. 1, paragraphs 0014-0021) Pharmaceutically acceptable salts of these compounds include the bromide salts. (p. 3, paragraph 0037)

Remington discloses that as part of the drug discovery process many different salts are prepared and evaluated. (p. 704, left column, second paragraph, right column, first and second paragraphs) During the process of salt selection various salt forms of a given active agent are explored and evaluated to determine which is the optimal form of

the drug. Hydrobromide is listed as being a pharmaceutically acceptable counterion with pKa and ClogP similar to hydrochloride. (p. 704, table 2) Parameters that depend on the counterion include solubility, dissolution, hygroscopicity, stability, and processing. (p. 705, right column, fourth paragraph) Multitiered and decision-tree approaches to salt selection and evaluation are discussed. (p. 712, left paragraph fifth column – right paragraph third paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to produce morphine-6-glucuronide hydrobromide by substituting the known hydrochloride salt with the bromide ion. It is obvious for one of ordinary skill in the art to substitute one known element of a prior art invention for another, where the art suggests the substitution. In the instant case, Gao et al. discloses that the bromide ion is suitable as a counterion for similar pharmaceutical compounds, and furthermore, Remington discloses that it is typical and routine in the art to make and evaluate a number of different salt forms of a given drug, including the hydrobromide form, in order to determine the optimal salt form for the desired application. Therefore one of ordinary skill in the art would have clearly been motivated to make and evaluate morphine-6-glucuronide hydrobromide as a pharmaceutical active agent. Furthermore, according to Pfizer v. Apotex (Fed. Cir. 2006-1261) in the case of a medicinal or pharmaceutical chemist developing an active agent for pharmaceutical use, "irrefutable evidence shows that a skilled chemist at the time would simply make known pharmaceutically-acceptable salts of whatever active ingredient with which he or she was working at the time." (p. 22, first paragraph) These salts would, as evidenced by Remington, include

the hydrobromide salt, which was a known pharmaceutically acceptable salt at the time of the invention. With regard to the fact that the anion under consideration was not commonly used in pharmaceutical active agents, the court stated, "That benzene sulphonate was only used in creating 0.25% of FDA-approved drugs is not highly probative, much less dispositive. Indeed, beyond hydrochloride, which was used in approximately 43% of approved drugs, almost all other salts could be characterized as 'rarely used.'" (p. 22, second paragraph)

Therefore the invention taken as a whole is *prima facie* obvious.

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hille et al. (US patent 5705186, cited in PTO-1449) in view of Merrill et al. (US patent 5593695, cited in PTO-892) in view of Remington. (Reference included with PTO-892) Hille et al. discloses transdermal compositions comprising morphine-6-glucuronide or its salts. (column 1, lines 45-55) Although all pharmaceutically acceptable salts are suitable for this invention, the hydrochloride salt is preferred. (column 3, lines 22-25) Hille et al. does not disclose a hydrobromide salt of morphine-6-glucuronide.

Merrill et al. discloses a pharmaceutical composition comprising morphine. (column 1, lines 35-47) Pharmaceutically acceptable forms or morphine include the hydrobromide salt. (column 1, line 58)

Remington discloses that as part of the drug discovery process many different salts are prepared and evaluated. (p. 704, left column, second paragraph, right column, first and second paragraphs) During the process of salt selection various salt forms of a

given active agent are explored and evaluated to determine which is the optimal form of the drug. Hydrobromide is listed as being a pharmaceutically acceptable counterion with pKa and ClogP similar to hydrochloride. (p. 704, table 2) Parameters that depend on the counterion include solubility, dissolution, hygroscopicity, stability, and processing. (p. 705, right column, fourth paragraph) Multitiered and decision-tree approaches to salt selection and evaluation are discussed. (p. 712, left paragraph fifth column – right paragraph third paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to produce morphine-6-glucuronide hydrobromide by substituting the known hydrochloride salt with the bromide ion. It is obvious for one of ordinary skill in the art to substitute one known element of a prior art invention for another, where the art suggests the substitution. In the instant case, Merrill et al. discloses that the bromide ion is suitable as a counterion for similar pharmaceutical compounds, and furthermore, Remington discloses that it is typical and routine in the art to make and evaluate a number of different salt forms of a given drug, including the hydrobromide form, in order to determine the optimal salt form for the desired application. Therefore one of ordinary skill in the art would have clearly been motivated to make and evaluate morphine-6-glucuronide hydrobromide as a pharmaceutical active agent. Furthermore, according to Pfizer v. Apotex (Fed. Cir. 2006-1261) in the case of a medicinal or pharmaceutical chemist developing an active agent for pharmaceutical use, "irrefutable evidence shows that a skilled chemist at the time would simply make known pharmaceutically-acceptable salts of whatever active ingredient with which he or she was working at the

time." (p. 22, first paragraph) These salts would, as evidenced by Remington, include the hydrobromide salt, which was a known pharmaceutically acceptable salt at the time of the invention. With regard to the fact that the anion under consideration was not commonly used in pharmaceutical active agents, the court stated, "That benzene sulphonate was only used in creating 0.25% of FDA-approved drugs is not highly probative, much less dispositive. Indeed, beyond hydrochloride, which was used in approximately 43% of approved drugs, almost all other salts could be characterized as 'rarely used.'" (p. 22, second paragraph)

Therefore the invention taken as a whole is *prima facie* obvious.

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hille et al. (US patent 5705186, cited in PTO-1449) in view of Berge et al. (Reference included with PTO-892) in view of Remington. (Reference included with PTO-892) Hille et al. discloses transdermal compositions comprising morphine-6-glucuronide or its salts. (column 1, lines 45-55) Although all pharmaceutically acceptable salts are suitable for this invention, the hydrochloride salt is preferred. (column 3, lines 22-25) Hille et al. does not disclose a hydrobromide salt of morphine-6-glucuronide.

Berge et al. discloses a number of commercially marketed pharmaceutically acceptable salts. (p. 2, table I) The hydrobromide salt is included as a pharmaceutically acceptable salt.

Remington discloses that as part of the drug discovery process many different salts are prepared and evaluated. (p. 704, left column, second paragraph, right column,

first and second paragraphs) During the process of salt selection various salt forms of a given active agent are explored and evaluated to determine which is the optimal form of the drug. Hydrobromide is listed as being a pharmaceutically acceptable counterion with pKa and ClogP similar to hydrochloride. (p. 704, table 2) Parameters that depend on the counterion include solubility, dissolution, hygroscopicity, stability, and processing. (p. 705, right column, fourth paragraph) Multitiered and decision-tree approaches to salt selection and evaluation are discussed. (p. 712, left paragraph fifth column – right paragraph third paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to produce morphine-6-glucuronide hydrobromide by substituting the known hydrochloride salt with the bromide ion. It is obvious for one of ordinary skill in the art to substitute one known element of a prior art invention for another, where the art suggests the substitution. In the instant case, Berge et al. discloses that the hydrobromide salt is suitable as a counterion for pharmaceutical compounds, and furthermore, Remington discloses that it is typical and routine in the art to make and evaluate a number of different salt forms of a given drug, including the hydrobromide form, in order to determine the optimal salt form for the desired application. Therefore one of ordinary skill in the art would have clearly been motivated to make and evaluate morphine-6-glucuronide hydrobromide as a pharmaceutical active agent. Furthermore, according to Pfizer v. Apotex (Fed. Cir. 2006-1261) in the case of a medicinal or pharmaceutical chemist developing an active agent for pharmaceutical use, "irrefutable evidence shows that a skilled chemist at the time would simply make known pharmaceutically-

acceptable salts of whatever active ingredient with which he or she was working at the time." (p. 22, first paragraph) These salts would, as evidenced by Remington, include the hydrobromide salt, which was a known pharmaceutically acceptable salt at the time of the invention. With regard to the fact that the anion under consideration was not commonly used in pharmaceutical active agents, the court stated, "That benzene sulphonate was only used in creating 0.25% of FDA-approved drugs is not highly probative, much less dispositive. Indeed, beyond hydrochloride, which was used in approximately 43% of approved drugs, almost all other salts could be characterized as 'rarely used.'" (p. 22, second paragraph)

Therefore the invention taken as a whole is *prima facie* obvious.

Conclusion

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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